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L1           2 S E4
               E FAGAN R/AU
L2          77 S E10-E12
               E PHELPS C/AU
L3           5 S E3,E5
               E PHELPS CHRIS/AU
L4          65 S E3,E5,E8
               E POWER C,AU
               E POWER C/AU
L5         155 S E3-E7,E17-E23
               E CHVATCHKO Y/AU
L6          47 S E3-E4
               E BOSCHERT U/AU
               E BOSCHERT U/AU
L7          29 S E3,E5
L8         287 S L1 OR L2 OR L3 OR L4 OR L5 OR L6 OR L7
               E CYTOKINE/CT
L9          57 S L8 AND CYTOKINE

     FILE 'HCAPLUS' ENTERED AT 12:19:32 ON 08 AUG 2005

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L9   ANSWER 1 OF 57  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:451220  HCAPLUS
DOCUMENT NUMBER:          143:6296
TITLE:                    Fusion proteins composed of extracellular domain (EC)
```

of human **cytokine** antagonist INSP052 and histidine tag or Fc region of human IgG1, their sequences and use in diagnosis and therapy of various diseases

INVENTOR(S): **Fagan, Richard Joseph**; Davids, Andrew Robert; **Phelps, Christopher Benjamin**; **Power, Christine**; **Boschert, Ursula**; **Chvatchko, Yolande**

PATENT ASSIGNEE(S): Ares Trading S. A., Switz.

SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005046714	A2	20050526	WO 2004-GB4772	20041112

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2003-26393 A 20031112

AB The invention provides fusion proteins composed of the extracellular domain (EC) of human Ig domain-containing cell surface recognition protein INSP052 and a heterologous protein, such as a signal peptide, histidine-tag, secreted protein or Fc region of human IgG1. The invention relates said human INSP052 proteins function as antagonists of **cytokine** expression and/or secretion. The invention also provides nucleic acid mols. encoding said INSP052 proteins. The invention further provides for the use of said INSP052 proteins and nucleic acid mols. in treatment of an autoimmune disease, skin disease, inflammatory disease, viral or acute liver disease, including alc. liver failure. Still further, the invention provides the amino acid and nucleic acid sequences of human INSP052(EC) proteins, and amino acid sequences of INSP052-histidine tag, and INSP052(EC)-IgG1 fusion proteins. In the examples, the invention demonstrated that INSP052(EC) was able to: (a) down-regulate secretion of **cytokines** TNFα, IL-4, and IL-2 from ConA-stimulated human PBMCs and CD4+ T cells; (b) protect mice mimicking fulminant hepatitis from liver injury; (c) down-regulate LPS-induced TFNα and IL-6 release in the blood; and (d) reduce ear swelling in mice with hapten induced contact hypersensitivity.

L9 ANSWER 2 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:376017 HCAPLUS

DOCUMENT NUMBER: 142:480266

TITLE: Multi-faceted strategies to combat disease by interference with the chemokine system

AUTHOR(S): Johnson, Zoee; Schwarz, Matthias; **Power, Christine A.**; Wells, Timothy N. C.; Proudfoot, Amanda E. I.

CORPORATE SOURCE: Serono Pharmaceutical Research Institute, Geneva, 1228, Switz.
SOURCE: Trends in Immunology (2005), 26(5), 268-274
CODEN: TIRMAE; ISSN: 1471-4906
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Inappropriate cell recruitment is a hallmark of all autoimmune, allergic and inflammatory diseases. The prevention of inflammation by interfering with cellular recruitment through the neutralization of **cytokines** and adhesion mols. has proven to be successful in the clinic. Chemokines are important potential targets owing to their central role in the cell recruitment process. Chemokines are unique among **cytokines** because they signal through seven transmembrane receptors, thus enabling the identification of small mol. inhibitors through high throughput screening. The object of this review is to discuss the validity and feasibility of targeting several points of therapeutic intervention offered by the chemokine system and to assess the state of play within the field to date.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:232637 HCAPLUS
DOCUMENT NUMBER: 142:309937
TITLE: Treatment of fibrotic disease
INVENTOR(S): **Power, Christine**; Lavrovsky, Yan
PATENT ASSIGNEE(S): Applied Research Systems Ars Holding N. V., Neth. Antilles
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005023288	A1	20050317	WO 2004-EP52077	20040907
WO 2005023288	C1	20050519		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2003-102723 A 20030908

AB The invention relates to the use of INSP035 for treatment and/or prevention of fibrotic diseases, in particular of scleroderma.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:60221 HCAPLUS

DOCUMENT NUMBER: 142:278451
TITLE: Circulating concentrations of interleukin-18, interleukin-18 binding protein, and γ interferon in patients with alcoholic hepatitis
AUTHOR(S): Spahr, Laurent; Garcia, Irene; Bresson-Hadni, Solange; Rubbia-Brandt, Laura; Guler, Reto; Olleros, Maria; **Chvatchko, Yolande**; Hadengue, Antoine
CORPORATE SOURCE: Gastroenterology and Hepatology Unit, University Hospital, Geneva, Switz.
SOURCE: Liver International (2004), 24(6), 582-587
CODEN: LIINCM; ISSN: 1478-3223
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Alc. hepatitis (AH) is associated with dysregulated inflammatory and immune responses, interleukin-18 (IL-18), described as γ interferon (γIFN)-inducible factor, and its natural antagonist, IL-18 binding protein (IL-18 BP), has not been fully studied in patients with AH. Thus, our aim was:. (i) to determine plasma values of IL-18, IL-18 BP, γIFN, and tumor necrosis factor α (TNF)-α in patients hospitalized for biopsy-proven AH;. (ii) to correlate these **cytokines** with the severity of AH, as assessed by Maddrey's discriminant function (DF), the degree of liver failure using the Child-Pugh score and blood neutrophils;. (iii) to compare **cytokines** values in survivors and non-survivors. **Cytokines** were measured using specific immunoassays within 7 days of admission. The diagnosis of AH was based on histol. in all cases. We studied 43 cirrhotic patients with a Maddrey's DF ≥32 (severe AH), 29 patients with a score <32 (non-severe AH), 12 patients with abstinent alc. cirrhosis, and 10 healthy subjects. IL-18 and TNFα were increased in severe AH as compared with healthy subjects. Plasma IL-18 BP was elevated in patients with severe and non-severe AH as compared with healthy subjects. γIFN did not differ between groups. In patients with severe and non-severe AH, IL-18, IL-18 BP, TNFα, but not γIFN, were pos. correlated to DF and Child-Pugh score. Neither IL-18 nor IL-18 BP correlated to TNFα. Patients who died (n = 10) during the hospitalization had higher IL-18 BP and TNFα at admission as compared with survivors (322 [172-504] vs. 222 [109-441] ng/mL; 7.5 [2.2-17.3] vs. 3 [0.6-20] pg/mL, P < 0.01, resp.). In cirrhotic patients with AH, IL-18, IL-18 BP, and TNFα correlate to the hepatitis severity and to the degree of liver failure. High IL-18 BP and TNFα at hospital admission in non-survivors suggest it may be of prognostic value.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1156584 HCAPLUS
DOCUMENT NUMBER: 142:92202
TITLE: Protein INSP037, gene and antibodies for screening of agonist/antagonist and for diagnosis and treatment of immune disease, infection, inflammation and proliferative disorder
INVENTOR(S): **Fagan, Richard Joseph**; **Chvatchko, Yolande**; Gutteridge, Alex; **Power, Christine**; **Boschert, Ursula**; **Phelps, Christopher Benjamin**
PATENT ASSIGNEE(S): Ares Trading S.A., Switz.
SOURCE: PCT Int. Appl., 110 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113379	A1	20041229	WO 2004-GB2641	20040621
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004106778	A1	20040603	US 2003-600790	20030620
PRIORITY APPLN. INFO.:			GB 2003-14456 A	20030620
			US 2003-600790 A	20030620
			GB 2001-30720 A	20011221

AB This invention relates to a protein, termed INSP037 or IPAAA44548, herein identified as an interferon gamma-like secreted protein containing the four helical bundle **cytokine** fold, and to the use of this protein and nucleic acid sequences from the encoding gene in the diagnosis, prevention and treatment of disease. The invention also relates to methods for identification or screening of agonists and antagonists of protein INSP037, genetic diagnosis, immunodiagnosis, and monitoring therapy. The disease includes cancer, inflammation, infection, allergy, immune and autoimmune disease, etc.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:303418 HCAPLUS
DOCUMENT NUMBER: 140:336463
TITLE: Osteopontin is upregulated during in vivo demyelination and remyelination and enhances myelin formation in vitro
AUTHOR(S): Selvaraju, Raghuram; Bernasconi, Lilia; Losberger, Christophe; Graber, Pierre; Kadi, Linda; Avellana-Adalid, Virginia; Picard-Riera, Nathalie; Van Evercooren, Anne Baron; Cirillo, Rocco; Kosco-Vilbois, Marie; Feger, Georg; Papoian, Ruben; **Boschert, Ursula**
CORPORATE SOURCE: Serono Pharmaceutical Research Institute, Department of Immunology, Ares-Serono International SA, Geneva, Switz.
SOURCE: Molecular and Cellular Neuroscience (2004), 25(4), 707-721
CODEN: MOCNED; ISSN: 1044-7431
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In vitro oligodendrocyte differentiation and the in vivo remyelination model was used, the cuprizone model, to identify genes regulating oligodendrocyte function and remyelination. One of the genes osteopontin

(opn) was identified, is a secreted glycoprotein with **cytokine** -like, chemotactic, and anti-apoptotic properties that contains an Arg-Gly-Asp (RGD) cell adhesion motif-mediating interactions with several integrins. Both microglia and astrocytes in demyelinating brain regions of cuprizone-fed mice expressed OPN protein. Recombinant OPN protein produced in a baculovirus expression system induced proliferation of both the rat CG-4 and the mouse Oli-neu oligodendrocyte precursor (OLP)-like cell lines in a dose-dependent manner. In addition, recombinant OPN treatment stimulated both myelin basic protein (MBP) synthesis and myelin sheath formation in mixed cortical cultures from embryonic mouse brain, an in vitro primary culture model of myelination. Interestingly, myelinating mixed cultures prepared from OPN-/- mice contained significantly less MBP compared to wild-type cultures after 17 days in culture. We propose that in the central nervous system, OPN may act as a novel regulator of myelination and remyelination.

REFERENCE COUNT: 97 THERE ARE 97 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:300402 HCAPLUS
DOCUMENT NUMBER: 141:52429
TITLE: Chemokine inhibition - why, when, where, which and how?
AUTHOR(S): Johnson, Z.; **Power, C. A.**; Weiss, C.; Rintelen, F.; Ji, H.; Ruckle, T.; Camps, M.; Wells, T. N. C.; Schwarz, M. K.; Proudfoot, A. E. I.; Rommel, C.
CORPORATE SOURCE: Serono Pharmaceutical Research Institute, Serono International, Geneva, CH 1228, Switz.
SOURCE: Biochemical Society Transactions (2004), 32(2), 366-377
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Chemokines are small chemoattractant **cytokines** that control a wide variety of biol. and pathol. processes, ranging from immunosurveillance to inflammation, and from viral infection to cancer. Genetic and pharmacol. studies have shown that chemokines are responsible for the excessive recruitment of leukocytes to inflammatory sites and damaged tissue. In the present paper, we discuss the rationale behind interfering with the chemokine system and introduce various points for therapeutic intervention using either protein-based or small-mol. inhibitors. Unlike other **cytokines**, chemokines signal via seven-transmembrane GPCRs (G-protein-coupled receptors), which are favored targets by the pharmaceutical industry, and, as such, they are the first **cytokines** for which small-mol.-receptor antagonists have been developed. In addition to the high-affinity receptor interaction, chemokines have an in vivo requirement to bind to GAGs (glycosaminoglycans) in order to mediate directional cell migration. Prevention of the GAG interaction has been shown to be a viable therapeutic strategy. Targeting chemokine intracellular signalling pathways offers an alternative small-mol. approach. One of the key signalling targets downstream of a variety of chemokine receptors identified to date is PI3Kγ (phosphoinositide 3-kinase γ), a member of the class I PI3K family. Thus, the chemokine system offers many potential entry points for innovative anti-inflammatory therapies for autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis and allergic contact dermatitis.

REFERENCE COUNT: 144 THERE ARE 144 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L9 ANSWER 8 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:294720 HCAPLUS
DOCUMENT NUMBER: 140:336202
TITLE: The human plasma proteome. A nonredundant list developed by combination of four separate sources
AUTHOR(S): Anderson, N. Leigh; Polanski, Malu; Pieper, Rembert; Gatlin, Tina; Tirumalai, Radhakrishna S.; Conrads, Thomas P.; Veenstra, Timothy D.; Adkins, Joshua N.; Pounds, Joel G.; **Fagan, Richard**; Lobley, Anna
CORPORATE SOURCE: The Plasma Proteome Institute, Washington, DC, 20009-3450, USA
SOURCE: Molecular and Cellular Proteomics (2004), 3(4), 311-326
CODEN: MCPOBS; ISSN: 1535-9476
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have merged four different views of the human plasma proteome, based on different methodologies, into a single nonredundant list of 1175 distinct gene products. The methodologies used were (1) literature search for proteins reported to occur in plasma or serum; (2) multidimensional chromatog. of proteins followed by two-dimensional electrophoresis and mass spectroscopy (MS) identification of resolved proteins; (3) tryptic digestion and multidimensional chromatog. of peptides followed by MS identification; and (4) tryptic digestion and multidimensional chromatog. of peptides from low-mol.-mass plasma components followed by MS identification. Of 1,175 nonredundant gene products, 195 were included in more than one of the four input datasets. Only 46 appeared in all four. Predictions of signal sequence and transmembrane domain occurrence, as well as Genome Ontol. annotation assignments, allowed characterization of the nonredundant list and comparison of the data sources. The "nonproteomic" literature (468 input proteins) is strongly biased toward signal sequence-containing extracellular proteins, while the three proteomics methods showed a much higher representation of cellular proteins, including nuclear, cytoplasmic, and kinesin complex proteins. **Cytokines** and protein hormones were almost completely absent from the proteomics data (presumably due to low abundance), while categories like DNA-binding proteins were almost entirely absent from the literature data (perhaps unexpected and therefore not sought). Most major categories of proteins in the human proteome are represented in plasma, with the distribution at successively deeper layers shifting from mostly extracellular to a distribution more like the whole (primarily cellular) proteome. The resulting non-redundant list confirms the presence of a number of interesting candidate marker proteins in plasma and serum.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:60555 HCAPLUS
DOCUMENT NUMBER: 140:127207
TITLE: Methods for the production and therapeutic uses of **cytokine** receptor INSP076 and ligands
INVENTOR(S): Rodrigues, Tania Maria; **Fagan, Richard Joseph**; **Phelps, Christopher Benjamin**; **Power, Christine**

PATENT ASSIGNEE(S): Ares Trading S.A., Switz.
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004007552	A1	20040122	WO 2003-GB3107	20030717
WO 2004007552	C1	20040415		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-16661 A 20020717

AB The invention is based on the discovery that the human protein referred to herein as INSP076 protein is a member of the **cytokine** receptor-type I family (hematopoietin receptor superfamily). Preferably, INSP076 functions as an IL-9 receptor or an IL-9 receptor-like protein. The INSP076 protein does not possess a transmembrane domain and accordingly the INSP076 protein is a potential soluble receptor. It is believed that the INSP076 protein may function as an IL-9 antagonist.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:991548 HCAPLUS
DOCUMENT NUMBER: 140:37105
TITLE: Protein and nucleotide sequences of human TNF-like protein and its use in diagnosis, prevention and treatment of disease
INVENTOR(S): **Power, Christine**; **Fagan, Richard Joseph**; **Phelps, Christopher Benjamin**; Mitter, Richard James
PATENT ASSIGNEE(S): Ares Trading S.A., Switz.
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003104278	A1	20031218	WO 2003-GB2510	20030611

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-13355 A 20020611

AB This invention relates to a protein BAB71417.1 herein identified as being a novel member of the TNF (tumor necrosis factor)-like family of **cytokines** and to use of this protein and nucleic acid sequence from the encoding gene in the diagnosis, prevention and treatment of disease.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:558577 HCAPLUS

DOCUMENT NUMBER: 139:178608

TITLE: IL-18 Binding Protein Protects Against Contact Hypersensitivity

AUTHOR(S): Plitz, Thomas; Saint-Mezard, Pierre; Satho, Masataka; Herren, Susanne; Waltzinger, Caroline; de Carvalho Bittencourt, Marcelo; Kosco-Vilbois, Marie H.; **Chvatchko, Yolande**

CORPORATE SOURCE: Department of Immunology, Serono Pharmaceutical Research Institute, Geneva, Switz.

SOURCE: Journal of Immunology (2003), 171(3), 1164-1171 CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Allergic contact dermatitis, the clin. manifestation of contact hypersensitivity, is one of the most common disorders of the skin. It is elicited upon multiple cutaneous re-exposure of sensitized individuals to the sensitizing agent. In this study, the authors demonstrate that using IL-18 binding protein (IL-18BP) to neutralize IL-18 significantly reduced clin. symptoms in a murine model of contact hypersensitivity. Furthermore, IL-18BP alleviated the relapses during established disease, as indicated by significant protection during re-exposure of mice that had previously undergone a contact hypersensitivity response without treatment. Although edema was not influenced, IL-18BP reduced the number of T cells homing to sites of inflammation, resulting in diminished local production of IFN-γ. Thus, by preventing the accumulation of effector T cells to the target tissue, IL-18BP appears to be a potent protective mediator to counter skin inflammation during contact hypersensitivity. Taken together with the evidence that IL-18 is present in tissue samples of the human disease, the authors' data reinforces IL-18BP as a candidate for this therapeutic indication.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:532690 HCAPLUS

DOCUMENT NUMBER: 139:81076

TITLE: Protein and nucleotide sequence of human secreted protein and its therapeutic uses

INVENTOR(S): **Fagan, Richard Joseph**; **Phelps, Christopher Benjamin**; Gutteridge, Alex; **Power, Christine**

PATENT ASSIGNEE(S): Ares Trading S.A., Switz.

SOURCE: PCT Int. Appl., 98 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055913	A2	20030710	WO 2002-GB5914	20021223
WO 2003055913	A3	20030821		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2470666	AA	20030710	CA 2002-2470666	20021223
EP 1468019	A2	20041020	EP 2002-805839	20021223
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002015284	A	20041214	BR 2002-15284	20021223
US 2005112618	A1	20050526	US 2004-872859	20040621
PRIORITY APPLN. INFO.:			GB 2001-30720 A	20011221
			WO 2002-GB5914 W	20021223

AB The invention relates to protein and cDNA sequence of novel secreted protein INSP037 of human. The protein has been identified as a member of the four helical bundle **cytokine** family and to the use of this protein and the nucleic acid sequence from the encoding gene in the diagnosis, prevention and treatment of disease.

L9 ANSWER 13 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:532689 HCAPLUS
DOCUMENT NUMBER: 139:96377
TITLE: Protein and nucleotide sequences of human secreted proteins
INVENTOR(S): **Fagan, Richard Joseph**; **Phelps, Christopher Benjamin**; Gutteridge, Alex; **Power, Christine**
PATENT ASSIGNEE(S): Ares Trading S.A., Switz.
SOURCE: PCT Int. Appl., 117 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055912	A2	20030710	WO 2002-GB5890	20021223
WO 2003055912	A3	20031231		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,				

UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2471306	AA	20030710	CA 2002-2471306	20021223
EP 1463756	A2	20041006	EP 2002-788245	20021223
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2005042731	A1	20050224	US 2004-873332	20040621
PRIORITY APPLN. INFO.:			GB 2001-30720 A	20011221
			WO 2002-GB5890 W	20021223

AB This invention relates to novel human proteins (INSP032, INSP033, INSP034, INSP036, INSP038), herein identified as members of the four helical bundle **cytokine** family. The invention relates to the use of these proteins and nucleic acid sequences from the encoding genes in the diagnosis, prevention and treatment of disease.

L9 ANSWER 14 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:532688 HCAPLUS
DOCUMENT NUMBER: 139:96376
TITLE: Cystine-knot fold protein family member INSP002, its cDNA and protein sequences, and expression vectors and therapeutic use thereof
INVENTOR(S): Davies, Mark Douglas; **Phelps, Christopher Benjamin**; **Fagan, Richard Joseph**; **Power, Christine**; Yorke, Melanie; Ibberson, Mark
PATENT ASSIGNEE(S): Ares Trading S.A., Switz.
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055911	A2	20030710	WO 2002-GB5865	20021220
WO 2003055911	A3	20030828		
WO 2003055911	C1	20031030		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2470781	AA	20030710	CA 2002-2470781	20021220
EP 1463754	A2	20041006	EP 2002-788225	20021220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, MK, CY, AL, TR, BG, CZ, EE, SK				
PRIORITY APPLN. INFO.:			GB 2001-30738 A	20011221
			WO 2002-GB5865 W	20021220

AB This invention relates to a novel protein (INSP002), herein identified as a secreted protein that is a member of the Dan family of the cystine-knot

fold **cytokine** superfamily and to the use of this protein and nucleic acid sequences from the encoding genes in the diagnosis, prevention and treatment of disease.

L9 ANSWER 15 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:511367 HCAPLUS
DOCUMENT NUMBER: 139:63799
TITLE: Leptin functional analogs and diagnostic and therapeutic uses
INVENTOR(S): **Fagan, Richard Joseph**; Gutteridge, Alex; **Phelps, Christopher Benjamin**; **Power, Christine**
PATENT ASSIGNEE(S): Ares Trading S. A., Switz.
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003054012	A2	20030703	WO 2002-GB5885	20021223
WO 2003054012	A3	20031120		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2470594	AA	20030703	CA 2002-2470594	20021223
EP 1468018	A2	20041020	EP 2002-788242	20021223
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2005106679	A1	20050519	US 2004-872598	20040621
PRIORITY APPLN. INFO.:			GB 2001-30720 A	20011221
			WO 2002-GB5885 W	20021223

AB This invention relates to novel protein INSP035, herein identified as a member of the four helical bundle **cytokine** family and to the use of this protein and the nucleic acid sequence from the encoding gene in the diagnosis, prevention and treatment of disease.

L9 ANSWER 16 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:756828 HCAPLUS
DOCUMENT NUMBER: 138:23483
TITLE: MIG-differential gene expression in mouse brain endothelial cells
AUTHOR(S): Ghersa, Paola; Gelati, Maurizio; Colinge, Jacques; Feger, Georg; **Power, Christine**; Papoian, Ruben; Salmaggi, Andrea
CORPORATE SOURCE: Serono Pharmaceutical Research Institute, Geneva, Switz.
SOURCE: NeuroReport (2002), 13(1), 9-14
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Different diseases of the CNS are associated with blood-brain barrier (BBB) damage and mononuclear cell infiltration. To study genes that may play a role in endothelial cell regulation in inflammatory CNS diseases, the authors performed differential gene expression (DGE) anal. using a mouse brain endothelial cell line. They found that interferon-γ (IFNγ)-induced monokine (MIG), a chemokine that plays a role in T lymphocyte and monocyte chemoattraction, is highly expressed in the presence of inflammatory **cytokines.** The authors show that MIG, produced by brain endothelial cells in vitro, is biol. active in attracting T lymphocytes and that it is possible to interfere with this mechanism of action using anti-MIG antibodies. The authors suggest that blocking MIG may be beneficial in CNS inflammation. The authors detected constitutive expression of the MIG receptor, CXCR3, on the surface of the endothelial cells and therefore hypothesize that it plays a role in maintaining the **cytokine** gradient at the region of CNS inflammation.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 17 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:612992 HCAPLUS
DOCUMENT NUMBER: 137:184206
TITLE: Cutting edge: a murine, IL-12-independent pathway of IFN-γ induction by gram-negative bacteria based on STAT4 activation by type I IFN and IL-18 signaling
AUTHOR(S): Freudenberg, Marina A.; Merlin, Thomas; Kalis, Christoph; **Chvatchko, Yolande**; Stubig, Hella; Galanos, Chris
CORPORATE SOURCE: Max-Planck-Institut fur Immunbiologie, Freiburg, 79108, Germany
SOURCE: Journal of Immunology (2002), 169(4), 1665-1668
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB IFN-αβ is a potent immunoregulatory **cytokine** involved in the defense against viral and bacterial infections. In this study, we describe an as yet undefined IFN-αβ-dependent pathway of IFN-γ induction in mice. This pathway is based on a synergism of IFN-αβ and IL-18, and is independent of IL-12 signaling yet dependent on STAT4. In contradiction to current dogma, we show further that IFN-αβ alone induces tyrosine phosphorylation of STAT4 in murine splenocytes of different mouse strains. This pathway participates in the induction of IFN-γ by Gram-neg. bacteria and is therefore expected to play a role whenever IFN-α or IFN-β and IL-18 are produced concomitantly during bacterial, viral, or other infections.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 18 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:571773 HCAPLUS
DOCUMENT NUMBER: 137:153743
TITLE: Airway hyperresponsiveness, but not airway remodeling, is attenuated during chronic pulmonary allergic responses to Aspergillus in CCR4-/- mice
AUTHOR(S): Schuh, Jane M.; **Power, Christine A.**; Proudfoot, Amanda E.; Kunkel, Steven L.; Lukacs,

Nicholas W.; Hogaboam, Cory M.
CORPORATE SOURCE: Department of Pathology, University of Michigan Medical School, Ann Arbor, MI, USA
SOURCE: FASEB Journal (2002), 16(10), 1313-1315, 10.1096/fj.02-0193fje
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The role of CC chemokine receptor 4 (CCR4) during the development and maintenance of Th2- type allergic airway disease is controversial. In this study, we examined the role of CCR4 in the chronic allergic airway response to live Aspergillus fumigatus spores, or conidia, in A. fumigatus-sensitized mice. After the conidia challenge, mice lacking CCR4 (CCR4-/- mice) exhibited significantly increased nos. of airway neutrophils and macrophages, and conidia were more rapidly eliminated from these mice compared with control CCR4 wild-type (CCR4+/+) mice. Significant airway hyperresponsiveness to i.v. methacholine was observed at day 3 in CCR4-/- mice, whereas at days 7 and 30, airway hyperresponsiveness was attenuated in these mice compared with control mice. A major reduction in peribronchial and airway eosinophilia was observed in CCR4-/- mice at all times after conidia challenge in contrast to CCR4+/+ mice. Further, whole lung levels of interleukin (IL) 4 and IL-5 were significantly increased in CCR4-/- mice at day 3, whereas these Th2 **cytokines** and IL-13 were significantly decreased at day 30 in CCR4-/- mice compared with their wild-type counterparts. Peribronchial fibrosis and goblet cell hyperplasia were similar in both groups of mice throughout the course of this model. In summary, CCR4 modulates both innate and acquired immune responses associated with chronic fungal asthma.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 19 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:429084 HCAPLUS
DOCUMENT NUMBER: 137:19397
TITLE: Novel sequence homologs of **cytokines** and cDNAs encoding them
INVENTOR(S): Gutteridge, Alex; **Fagan, Richard Joseph; Phelps, Christopher Benjamin**
PATENT ASSIGNEE(S): Inpharmatica Limited, UK
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002044382	A1	20020606	WO 2001-GB5245	20011128
WO 2002044382	C1	20020718		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2429819	AA	20020606	CA 2001-2429819 20011128
AU 2002020838	A5	20020611	AU 2002-20838 20011128
EP 1337642	A1	20030827	EP 2001-998640 20011128

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

US 2004053297	A1	20040318	US 2003-445641 20030527

PRIORITY APPLN. INFO.: GB 2000-28971 A 20001128
WO 2001-GB5245 W 20011128

AB This invention relates to proteins, termed Q14507, CAA53971.2 and CAC17141.1 herein identified as **cytokines** and to the use of these proteins and nucleic acid sequences from the encoding genes in the diagnosis, prevention and treatment of disease. New proteins identified as sequence homologs of **cytokines** are identified by datamining of sequence databases for relatives of angiogenin. The proteins and genes encoding them may be useful in the diagnosis and treatment of disease. Identification of angiogenin homologs using the three dimensional structure of angiogenin is described.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 20 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:390524 HCAPLUS
DOCUMENT NUMBER: 137:32026
TITLE: IL-18-independent cytotoxic T lymphocyte activation and IFN-γ production during experimental acute graft-versus-host disease
AUTHOR(S): Arnold, Diana; Wasem, Christoph; Juillard, Pierre; Graber, Pierre; Cima, Igor; Frutschi, Corina; Herren, Simon; Jakob, Sabine; Alouani, Sami; Mueller, Christoph; **Chvatchko, Yolande**; Brunner, Thomas
CORPORATE SOURCE: Division of Immunopathology, Institute of Pathology, University of Bern, Bern, 3010, Switz.
SOURCE: International Immunology (2002), 14(5), 503-511
CODEN: INIMEN; ISSN: 0953-8178
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Acute graft-vs.-host disease (GvHD) is a serious complication after allogeneic bone marrow transplantation. Donor-derived T cells infiltrate recipient target organs and cause severe tissue damage, often leading to death of the affected patient. Tissue destruction is a direct result of donor CD8+ T cell activation and cell-mediated cytotoxicity. IL-18 is a novel pro-inflammatory **cytokine** with potent Th1 immune response-promoting and cytotoxic T lymphocyte (CTL)-inducing activity. IL-18 is strongly induced in exptl. mouse models and human patients with acute GvHD. However, the precise role of IL-18 in the development of acute GvHD is still unknown. Here, the authors have used IL-18-binding protein, a soluble IL-18 decoy receptor, to specifically neutralize IL-18 in vivo and in vitro. Their results demonstrate that IL-18 is induced during GvHD. However, its effect in the induction of GvHD appears to be redundant, since neutralization of IL-18 does not alter any disease parameter analyzed. The study further shows that IFN-γ production and CTL induction upon activation by T cell mitogens or by alloantigen does not involve IL-18-mediated amplification, in contrast to lipopolysaccharide-induced IFN-γ production Thus, IL-18 expression

correlates with the course of GvHD; however, its effect is dispensable for IFN-γ and CTL induction for the initiation phase of this disease, most likely due to direct, IL-18-independent, CTL activation.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 21 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:276165 HCAPLUS
DOCUMENT NUMBER: 136:275148
TITLE: Human CC1 and CC2 **cytokine** sequence homologs and their potential use in diagnosis and treatment of immune system diseases
INVENTOR(S): **Fagan, Richard Joseph**; **Phelps, Christopher Benjamin**; Gutteridge, Alex
PATENT ASSIGNEE(S): Impharmatica Limited, UK
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002029062	A2	20020411	WO 2001-GB4412	20011004
WO 2002029062	A3	20020808		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001092077	A5	20020415	AU 2001-92077	20011004
PRIORITY APPLN. INFO.:			GB 2000-24283 A	20001004
			WO 2001-GB4412 W	20011004

AB This invention relates to novel proteins, identified by sequence homol., CC1 and CC2 **cytokines**, and the potential use of these proteins and nucleic acid sequences from the encoding genes in the diagnosis, prevention and treatment of immune disorders. Potential agonists or antagonists of CC1 and CC2 polypeptides and methods to identify these agents form another embodiment of the invention. Oligoncucleotide probes and primers may be used to detect mutations in nucleic acids encoding CC1 and CC2 **cytokines.** Furthermore, kits that contain these oligonucleotide probes and primers as well as antibodies may be used for detection of the proteins in tissue samples. Also, these test kits may contain an agent for digesting unhybridized RNA in a third container for diagnosis of disease. The proteins have potential uses as vaccines or in pharmaceutical compns. for treatment of immune system diseases.

L9 ANSWER 22 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:262078 HCAPLUS
DOCUMENT NUMBER: 136:354094
TITLE: IL-18-binding protein expression by endothelial cells and macrophages is up-regulated during active Crohn's disease
AUTHOR(S): Corbaz, Anne; ten Hove, Tessa; Herren, Suzanne;

Graber, Pierre; Schwartsburd, Boris; Belzer, Ilana; Harrison, Jillian; Plitz, Thomas; Kosco-Vilbois, Marie H.; Kim, Soo-Hyun; Dinarello, Charles A.; Novick, Daniela; Van Deventer, Sander; **Chvatchko, Yolande**

CORPORATE SOURCE: Department of Experimental Biology and Pharmacology, Serono Pharmaceutical Research Institute, Geneva, 1228, Switz.

SOURCE: Journal of Immunology (2002), 168(7), 3608-3616
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pathogenesis of Crohn's disease (CD) remains under intense investigation. Increasing evidence suggests a role for mature IL-18 in the induction of proinflammatory **cytokines** and Th1 polarization in CD lesions. The aim here was to investigate the contribution of the IL-18-neutralizing (a and c) and non-neutralizing (b and d) isoforms of IL-18-binding protein (IL-18BP) during active CD. Intestinal endothelial cells and macrophages were the major source of IL-18BP within the submucosa, and this IL-18BP production was also relevant to other types of endothelial cells (HUVEC) and macrophages (peripheral monocytes). IL-18BP messenger transcript and protein were increased in surgically resected specimens from active CD compared with control patients, correlating with an up-regulation of IL-18. Anal. of the expression of the 4 IL-18BP isoforms as well as being free or bound to IL-18 was reported and revealed that unbound IL-18BP isoforms a and c and inactive isoform d were present in specimens from active CD and control patients while isoform b was not detected. IL-18/IL-18BP complex was also detected. Interestingly, although most was complexed, free mature IL-18 could still be detected in active CD specimens even in the presence of the IL-18BP isoform a/c. Thus, the appropriate neutralizing isoforms are present in the intestinal tissue of patients with active CD, highlighting the complexity of IL-18/IL-18BP biol.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 23 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:16928 HCAPLUS
DOCUMENT NUMBER: 137:4758

TITLE: Blockade of endogenous IL-18 ameliorates TNBS-induced colitis by decreasing local TNF-α production in mice

AUTHOR(S): Ten Hove, Tessa; Corbaz, Anne; Amitai, Hagit; Aloni, Shuki; Belzer, Ilana; Graber, Pierre; Drillenburg, Paul; Van Deventer, Sander J. H.; **Chvatchko, Yolande**; Te Velde, Anje A.

CORPORATE SOURCE: Laboratory of Experimental Internal Medicine, Academic Medical Centre, Amsterdam, Neth.

SOURCE: Gastroenterology (2001), 121(6), 1372-1379
CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Interleukin (IL) 18 has proinflammatory effects. It plays a pivotal role in Th1 responses, but its proinflammatory activities extend beyond Th1 cells, including macrophages and production of tumor necrosis factor (TNF) α and IL-1β. IL-18 is up-regulated in colonic specimens of patients with Crohn's disease. The goal here was to evaluate the role of

IL-18. Activity of IL-18 was neutralized using recombinant human IL-18 binding protein isoform a (rhIL-18BPa) in trinitrobenzene sulfonic acid (TNBS)-induced colitis. Mice treated daily with rhIL-18BPa (8 mg/kg) had redns. in clin. score, body weight loss, and colon weight increase compared with saline-treated mice. Histol. anal. showed that rhIL-18BPa-treated mice developed only mild colitis without signs of ulceration, with a mean total score of 9.8 points compared with 15.9 points observed in saline-treated mice with colitis. Anal. of **cytokine** levels in colon homogenates showed a decrease in TNF-α, IL-6, and IL-1β after rhIL-18BPa treatment but no effect on interferon γ. The therapeutic potential of rhIL-18BPa treatment was confirmed in TNBS mice that were treated only on days 8 and 9 after the start of the experiment In these mice, redns. in total colitis score and colon weight were also observed Thus, inhibition of rhIL-18BPa bioactivity, via rhIL-18BPa, may be beneficial for the treatment of IBD.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 24 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:920017 HCAPLUS

DOCUMENT NUMBER: 136:165821

TITLE: Therapeutic effect of neutralizing endogenous IL-18 activity in the collagen-induced model of arthritis

AUTHOR(S): Plater-Zyberk, Christine; Joosten, Leo A. B.; Helsen, Monique M. A.; Sattonnet-Roche, Pascale; Siegfried, Christiane; Alouani, Sami; Van de Loo, Fons A. J.; Graber, Pierre; Aloni, Shuki; Cirillo, Rocco; Lubberts, Erik; Dinarello, Charles A.; Van den Berg, Wim B.; **Chvatchko, Yolande**

CORPORATE SOURCE: Serono Pharmaceutical Research Institute, Geneva, Switz.

SOURCE: Journal of Clinical Investigation (2001), 108(12), 1825-1832
CODEN: JCINAO; ISSN: 0021-9738

PUBLISHER: American Society for Clinical Investigation

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Two distinct IL-18 neutralizing strategies, i.e. a rabbit polyclonal anti-mouse IL-18 IgG and a recombinant human IL-18 binding protein (rhIL-18BP), were used to treat collagen-induced-arthritic DBA/1 mice after clin. onset of disease. The therapeutic efficacy of neutralizing endogenous IL-18 was assessed using different pathol. parameters of disease progression. The clin. severity in mice undergoing collagen-induced arthritis was significantly reduced after treatment with both IL-18 neutralizing agents compared to placebo treated mice. Attenuation of the disease was associated with reduced cartilage erosion evident on histol. The decreased cartilage degradation was further documented by a significant reduction in the levels of circulating cartilage oligomeric matrix protein (an indicator of cartilage turnover). Both strategies efficiently slowed disease progression, but only anti-IL-18 IgG treatment significantly decreased an established synovitis. Serum levels of IL-6 were significantly reduced with both neutralizing strategies. In vitro, neutralizing IL-18 resulted in a significant inhibition of TNF-α, IL-6, and IFN-γ secretion by macrophages. These results demonstrate that neutralizing endogenous IL-18 is therapeutically efficacious in the murine model of collagen-induced arthritis. IL-18 neutralizing antibody or rhIL-18BP could therefore represent new disease-modifying anti-rheumatic drugs that warrant testing in clin. trials in patients with

rheumatoid arthritis.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 25 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:891111 HCAPLUS
DOCUMENT NUMBER: 137:45044
TITLE: Bacterial Wall Products Induce Downregulation of Vascular Endothelial Growth Factor Receptors on Endothelial Cells via a CD14-Dependent Mechanism: Implications for Surgical Wound Healing
AUTHOR(S): **Power, C.**; Wang, J. H.; Sookhai, S.; Street, J. T.; Redmond, H. P.
CORPORATE SOURCE: Department of Academic Surgery, Cork University Hospital, Wilton, Cork, Ire.
SOURCE: Journal of Surgical Research (2001), 101(2), 138-145
CODEN: JSGRA2; ISSN: 0022-4804
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Introduction. Vascular endothelial growth factor (VEGF) is a potent mitogenic **cytokine** which has been identified as the principal polypeptide growth factor influencing endothelial cell (EC) migration and proliferation. Ordered progression of these two processes is an absolute prerequisite for initiating and maintaining the proliferative phase of wound healing. The response of ECs to circulating VEGF is determined by, and directly proportional to, the functional expression of VEGF receptors (KDR/Flt-1) on the EC surface membrane. Systemic sepsis and wound contamination due to bacterial infection are associated with significant retardation of the proliferative phase of wound repair. The effects of the Gram-neg. bacterial wall components lipopolysaccharide (LPS) and bacterial lipoprotein (BLP) on VEGF receptor function and expression are unknown and may represent an important biol. mechanism predisposing to delayed wound healing in the presence of localized or systemic sepsis. Materials and methods. We designed a series of in vitro expts. investigating this phenomenon and its potential implications for infective wound repair. VEGF receptor d. on ECs in the presence of LPS and BLP was assessed using flow cytometry. These parameters were assessed in hypoxic conditions as well as in normoxia. The contribution of CD14 was evaluated using recombinant human (rh) CD14. EC proliferation in response to VEGF was quantified in the presence and absence of LPS and BLP. Results. Flow cytometric anal. revealed that LPS and BLP have profoundly repressive effects on VEGF receptor d. in normoxic and, more pertinently, hypoxic conditions. The observed downregulation of constitutive and inducible VEGF receptor expression on ECs was not due to any directly cytotoxic effect of LPS and BLP on ECs, as measured by cell viability and apoptosis assays. We identified a pivotal role for soluble/serum CD14, a highly specific bacterial wall product receptor, in mediating these effects. The decreased VEGF receptor d. on ECs accruing from the presence of bacterial wall products resulted in EC hyporesponsiveness to rhVEGF and significant abolition of VEGF-directed EC proliferation. Conclusion. These findings suggest that the well-recognized relationship between bacterial sepsis and attenuated wound healing may be due, in part, to the directly suppressive effects of bacterial wall components on EC VEGF receptor expression and, consequently, EC proliferation. (c) 2001 Academic Press.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 26 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:803249 HCAPLUS
DOCUMENT NUMBER: 136:308197
TITLE: Expression of interleukin-18 in human atherosclerotic plaques and relation to plaque instability
AUTHOR(S): Mallat, Ziad; Corbaz, Anne; Scoazec, Alexandra; Besnard, Sandrine; Leseche, Guy; **Chvatchko, Yolande**; Tedgui, Alain
CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale, INSERM U541, Institut Federatif de Recherche Circulation Paris VII, Hopital Lariboisiere, Paris, 75010, Fr.
SOURCE: Circulation (2001), 104(14), 1598-1603
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Interleukin (IL)-18 is a potent proinflammatory **cytokine** with potential atherogenic properties. Its expression and role in atherosclerosis, however, are unknown. Here, the authors examined stable and unstable human carotid atherosclerotic plaques retrieved by endarterectomy for the presence of IL-18 using reverse transcription-polymerase chain reaction (PCR), Western blot, and immunohistochem. techniques. IL-18 was highly expressed in the atherosclerotic plaques compared with control normal arteries and was localized mainly in plaque macrophages. IL-18 receptor was also upregulated in plaque macrophages and endothelial cells, suggesting potential biol. effects. To examine the role of IL-18 in atherosclerosis, the authors determined the relation between IL-18 mRNA expression and signs of plaque instability using real-time quant. PCR. Interestingly, higher levels of IL-18 mRNA were found in symptomatic (unstable) plaques than asymptomatic (stable) plaques. These results suggest, for the first time, a major role for IL-18 in atherosclerotic plaque destabilization leading to acute ischemic syndromes.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 27 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:581347 HCAPLUS
DOCUMENT NUMBER: 135:287398
TITLE: A novel IL-18BP ELISA shows elevated serum IL-18BP in sepsis and extensive decrease of free IL-18
AUTHOR(S): Novick, Daniela; Schwartsburd, Boris; Pinkus, Ron; Suissa, Dan; Belzer, Ilana; Sthoeger, Zev; Keane, William F.; **Chvatchko, Yolande**; Kim, Soo-Hyun; Fantuzzi, Giamila; Dinarello, Charles A.; Rubinstein, Menachem
CORPORATE SOURCE: Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: Cytokine (2001), 14(6), 334-342
CODEN: CYTIE9; ISSN: 1043-4666
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB IL-18 binding protein (IL-18BP) is a circulating antagonist of the proinflammatory Th1 **cytokine** IL-18. It effectively blocks IL-18 by forming a 1:1 high affinity (Kd=400 pM) complex, exhibiting a very low dissociation rate. We have developed a sandwich ELISA for IL-18BPa and determined its limit of detection (62 pg/mL). Interference by IL-18 and related

cytokines, as well as cross reactivity with other IL-18BP isoforms (b, c, and d) were determined Using this ELISA, we measured serum IL-18BPa in large cohorts of healthy individuals and in septic patients. Serum IL-18BPa in healthy individuals was 2.15±0.15 ng/mL (range 0.5-7 ng/mL). In sepsis, the level rose to 21.9±1.44 ng/mL (range 4-132 ng/mL). Total IL-18 was measured in the same sera by an electrochemiluminescence assay and free IL-18 was calculated based on the mass action law. Total IL-18 was low in healthy individuals (64±17 pg/mL) and most of it (.apprx.85%) was in its free form. Total IL-18 and IL-18BPa were both elevated in sepsis patients upon admission (1.5±0.4 ng/mL and 28.6±4.5 ng/mL, resp.). At these levels, most of the IL-18 is bound to IL-18BPa, however the remaining free IL-18 is still higher than in healthy individuals. We conclude that IL-18BPa considerably inhibits circulating IL-18 in sepsis. Yet, exogenous administration of IL-18BPa may further reduce circulating IL-18 activity. (c) 2001 Academic Press.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 28 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:543615 HCAPLUS
DOCUMENT NUMBER: 135:255692
TITLE: The chemokine system: novel broad-spectrum therapeutic targets
AUTHOR(S): **Power, Christine A.**; El Proudfoot, Amanda
CORPORATE SOURCE: Serono Pharmaceutical Research Institute, Geneva, Switz.
SOURCE: Current Opinion in Pharmacology (2001), 1(4), 417-424
CODEN: COPUBK; ISSN: 1471-4892
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 47 refs. Chemokines are **cytokines** that specifically direct the trafficking of immune cells in the body. They offer a novel point of therapeutic intervention, as inhibiting specific chemokines and receptors could prevent the excessive recruitment of leukocytes to sites of inflammation. This approach could be considered to act upstream of the therapies used today which, for the most part, act on the cells already at the site of inflammation. The receptors for chemokines are G-protein-coupled seven-transmembrane receptors, which are particularly tractable for the pharmaceutical industry. The search for small-mol. inhibitors of these receptors has been fruitful and the nos. of patents and, more recently, peer-reviewed publications are growing rapidly. The first clin. trial was initiated this year, so although it is too soon to be able to report these results the authors hope to see the outcome of this research in the near future.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 29 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:790144 HCAPLUS
DOCUMENT NUMBER: 133:349154
TITLE: CCR4 antagonists for treatment of septic shock
INVENTOR(S): **Power, Christina A.**; Chivatchko, Yolande
PATENT ASSIGNEE(S): Applied Research Systems ARS Holding N.V., Neth. Antilles
SOURCE: Eur. Pat. Appl., 20 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1050307	A1	20001108	EP 1999-108954	19990506
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
WO 2000067791	A1	20001116	WO 2000-EP4018	20000504
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1176980	A1	20020206	EP 2000-927140	20000504
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002544171	T2	20021224	JP 2000-616816	20000504
PRIORITY APPLN. INFO.:			EP 1999-108954 A	19990506
			WO 2000-EP4018 W	20000504

AB The authors disclose the **cytokine** and cellular responses to lipopolysaccharide administration in mice having a targeted disruption of the CCR4 gene. CCR4 receptor antagonists (e.g., antibodies) are proposed for the treatment and/or prevention of septic shock.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 30 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:726387 HCAPLUS
DOCUMENT NUMBER: 134:265097
TITLE: Lethal Mycobacterium bovis Bacillus Calmette Guerin infection in nitric oxide synthase 2-deficient mice: Cell-mediated immunity requires nitric oxide synthase 2
AUTHOR(S): Garcia, Irene; Guler, Reto; Vesin, Dominique; Olleros, Maria L.; Vassalli, Pierre; **Chvatchko, Yolande**; Jacobs, Muazzam; Ryffel, Bernhard
CORPORATE SOURCE: Department of Pathology Centre Medical Universitaire, University of Geneva, Geneva, 1211/4, Switz.
SOURCE: Laboratory Investigation (2000), 80(9), 1385-1397
CODEN: LAINAW; ISSN: 0023-6837
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The role of nitric oxide (NO) in Mycobacterium bovis Bacillus Calmette Guerin (BCG) infection was investigated using nitric oxide synthase 2 (nos2)-deficient mice, because NO plays a pivotal protective role in M. tuberculosis infection. Nos2-deficient mice were unable to eliminate BCG and succumbed within 8 to 12 wk to BCG infection (106 CFU) with cachexia and pneumonia, whereas all infected wild-type mice survived. The greatest mycobacterial loads were observed in lung and spleen. Nos2-deficient mice developed large granulomas consisting of macrophages and activated T cells and caseous necrotic lesions in spleen. The macrophages in granulomas from nos2-deficient mice had reduced acid phosphatase activities,

suggesting that NO is required for macrophage activation. The absence of NOS2 affected the **cytokine** production of the Th1 type of immune response, except IL-18. Serum amts. of IL-12p40 were increased and IFN-γ was decreased compared with wild-type mice. The lack of NOS2 resulted in an overprodn. of TNF, observed throughout the infection period. Addnl., TNFR1 and TNFR2 shedding was altered compared with wild-type mice. Up-regulation of TNF may be compensatory for the lack of NOS2. The late neutralization of TNF by soluble TNF receptors resulted in heightened disease severity and accelerated death in nos2-deficient mice but had no effect in wild-type mice. In conclusion, the inability of nos2-deficient mice to kill M. bovis BCG resulted in an accumulation of mycobacteria with a dramatic activation of the immune system and overprodn. of pro-inflammatory **cytokines**, which resulted in death.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 31 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:321519 HCAPLUS
DOCUMENT NUMBER: 131:142991
TITLE: Dysregulation of adenosine A1 receptor-mediated **cytokine** expression in peripheral blood mononuclear cells from multiple sclerosis patients
AUTHOR(S): Mayne, M.; Shepel, P. N.; Jiang, Y.; Geiger, J. D.; **Power, C.**
CORPORATE SOURCE: Departments of Pharmacology and Therapeutics, University of Manitoba, Winnipeg, MB, Can.
SOURCE: Annals of Neurology (1999), 45(5), 633-639
CODEN: ANNED3; ISSN: 0364-5134
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Cytokines**, including tumor necrosis factor-α (TNFα) and interleukin-6 (IL-6), have been implicated in the pathogenesis of multiple sclerosis (MS). The production and release of these **cytokines** are regulated in part by specific purinergic (adenosine) cell surface receptors. To determine the extent to which the adenosine A1 receptor influenced **cytokine** expression in peripheral blood mononuclear cells (PBMCs) from MS and control patients, we measured plasma adenosine and TNFα levels, A1 receptor mRNA (mRNA) and protein amts., and the effects of activation of A1 receptors on TNFα and IL-6 production by PBMCs. Plasma levels of TNFα were significantly higher and adenosine levels were significantly lower in MS patients compared with control subjects. Levels of TNFα and IL-6 in mitogen-stimulated PBMC culture supernatants from MS patients or control patients were similar. Conversely, treatment of PBMCs with the adenosine A1 receptor agonist R-phenylisopropyladenosine (R-PIA) (1 μM) significantly inhibited mitogen-stimulated production of TNFα but not IL-6 in control subjects and significantly inhibited production of IL-6 but not TNFα in MS patients. The effects of R-PIA were selectively blocked by the A1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX). A1 receptor protein levels were decreased significantly in PBMCs from MS patients. Taken together, these results suggest that decreased levels of adenosine and its A1 receptor modulate TNFα and IL-6 levels and may contribute to the pathogenesis of MS.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 32 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:33082 HCAPLUS

DOCUMENT NUMBER: 130:195604
TITLE: Up-regulation of CCR1 and CCR3 and induction of chemotaxis to CC chemokines by IFN-γ in human neutrophils
AUTHOR(S): Bonecchi, Raffaella; Polentarutti, Nadia; Luini, Walter; Borsatti, Alessandro; Bernasconi, Sergio; Locati, Massimo; **Power, Christine**; Proudfoot, Amanda; Wells, Timothy N. C.; Mackay, Charles; Mantovani, Alberto; Sozzani, Silvano
CORPORATE SOURCE: Istituto di Ricerche Farmacologiche "Mario Negri", Milan, 20157, Italy
SOURCE: Journal of Immunology (1999), 162(1), 474-479
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human neutrophils (polymorphonuclear leukocytes; PMN) respond to some CXC chemokines but do not migrate to CC chemokines. Recent work has shown that chemokine receptors can be modulated by inflammatory **cytokines.** In this study, the effect of IFN-γ, a prototypic Th1 **cytokine**, on chemokine receptor expression in PMN was investigated. IFN-γ caused a rapid (.apprx.1 h) and concentration-dependent increase of CCR1 and CCR3 mRNA. The expression of CCR2, CCR5, and CXCR1-4 was not augmented. IFN-γ-treated PMN, but not control cells, expressed specific binding sites for labeled monocyte-chemotactic protein (MCP)-3 and migrated to macrophage-inflammatory protein (MIP)-1α, RANTES, MCP-3, MIP-5/HCC2, and eotaxin. 7B11, a mAb for CCR3, inhibited the chemotactic response of IFN-γ-treated PMN to eotaxin, and aminoxypentane-RANTES blocked PMN migration to RANTES. These results suggest that the selectivity of certain chemokines for their target cells may be altered by **cytokines** produced within an inflammatory context. Since PMN may play a role in orienting immunity toward Th1 responses, it is possible to speculate that IFN-γ not only promotes Th1 differentiation directly, but also reorients the functional significance of Th2 effector **cytokines** by broadening the spectrum of their action to include PMN.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 33 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:669856 HCAPLUS
DOCUMENT NUMBER: 127:317647
TITLE: Induction of the dual specificity phosphatase PAC1 in rat brain following seizure activity
AUTHOR(S): **Boschert, Ursula**; Muda, Marco; Camps, Montserrat; Dickinson, Robin; Arkinstall, Steve
CORPORATE SOURCE: Geneva Biomedical Research Institute, Glaxo Wellcome Research and Development SA, Plan-les-Outeas/Geneva, 1228, Switz.
SOURCE: NeuroReport (1997), 8(14), 3077-3080
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recurrent seizure activity leads to delayed neuronal death as well as to inflammatory responses involving microglia in hippocampal subfields CA1, CA3 and CA4. Since mitogen-activated protein (MAP) kinases control

neuronal apoptosis and trigger generation of inflammatory **cytokines**, their activation state could determine seizure-related brain damage. PAC1 is a dual-specificity protein phosphatase inactivating MAP kinases which is undetectable in normal brain. Despite this, kainic acid-induced seizure activity lead to rapid (.apprx.3 h) but transient appearance of PAC1 mRNA in granule cells of the dentate gyrus as well as in pyramidal CA1 neurons. This pattern changed with time and after 2-3 days PAC1 was induced in dying CA1 and CA3 neurons. At this time PAC1 mRNA was also expressed in white matter microglia as well as in microglia invading the damaged hippocampus. PAC1 may play an important role controlling MAP kinase involvement in both neuronal death and neuro-inflammation following excitotoxic damage.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 34 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:622387 HCAPLUS
DOCUMENT NUMBER: 127:306439
TITLE: Characterization of macrophage inflammatory protein-5/human CC **cytokine**-2, a member of the macrophage-inflammatory-protein family of chemokines
AUTHOR(S): Coulin, Florence; **Power, Christine A.**; Alouani, Sami; Peitsch, Manuel C.; Schroeder, Jens-Michael; Moshizuki, Mizuru; Clark-Lewis, Ian; Wells, Timothy N. C.
CORPORATE SOURCE: Geneva Biomedical Research Institute, Geneva, CH-1228, Switz.
SOURCE: European Journal of Biochemistry (1997), 248(2), 507-515
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A human monocyte-activating CC chemokine has been identified based on sequences in an expressed sequence tag (EST) cDNA database. The protein shows highest sequence identity to the macrophage inflammatory protein (MIP) group of chemokines, particularly MIP-3 (76.7%) and MIP-1α (75.4%), and has been named MIP-5. Model building confirms that the protein has a similar three dimensional structure to other chemokines, but has an addnl. third disulfide bond. Northern blot anal. and reverse-transcriptase PCR show that the mRNA for MIP-5 is expressed at a high levels in liver, intestine and in lung leukocytes. MIP-5 induces chemotaxis of human monocytes, T-lymphocytes and, to a lesser degree, eosinophils at nanomolar concns.; it has no effect on neutrophil migration. In receptor-binding assays, MIP-5 shows IC50 values of 12 nM for competition with 125I-MIP-1α for binding to CC-chemokine receptor (CCR) 1, and 2.5 nM for competition with 125I-MCP-3 for binding to CCR3. It shows no ability to compete with ligand for binding to the two interleukin (IL)-8 receptors (CXC-chemokine receptors 1 and 2) or to CCR2, CCR4 or CCR5. Consistent with this binding data, MIP-5 was only able to induce calcium fluxes in CHO cells stably transfected with CCR1 or CCR3.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 35 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:609163 HCAPLUS
DOCUMENT NUMBER: 127:291894

TITLE: Cloning and characterization of a specific receptor for the novel CC chemokine MIP-3α from lung dendritic cells

AUTHOR(S): **Power, Christine A.**; Church, Dennis J.; Meyer, Alexandra; Alouani, Sami; Proudfoot, Amanda E. I.; Clark-Lewis, Ian; Sozzani, Silvano; Mantovani, Alberto; Wells, Timothy N. C.

CORPORATE SOURCE: Geneva Biomedical Research Institute, Glaxo Wellcome Research and Development, Geneva, Switz.

SOURCE: Journal of Experimental Medicine (1997), 186(6), 825-835
CODEN: JEMEAV; ISSN: 0022-1007

PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Dendritic cells are potent antigen-presenting cells involved in the initiation of immune responses. The trafficking of these cells to tissues and lymph nodes is mediated by members of the chemokine family. Recently, a novel CC chemokine known as MIP-3α or liver and activation-regulated chemokine has been identified from the EMBL/GenBank/DDBJ expressed sequence tag database. In the present study, the authors have shown that the mRNA for MIP-3α is expressed predominantly in inflamed and mucosal tissues. MIP-3α produced either synthetically or by human embryonic kidney 293 cells is chemotactic for CD34+-derived dendritic cells and T cells, but is inactive on monocytes and neutrophils. MIP-3α was unable to displace the binding of specific CC or CXC chemokines to stable cell lines expressing their resp. high affinity receptors, namely CCR1-5 and CXCR1 and CXCR2, suggesting that MIP-3α acts through a novel CC chemokine receptor. Therefore, the authors used degenerate oligonucleotide-based reverse transcriptase PCR to identify candidate MIP-3α receptors in lung dendritic cells. The authors' results show that the orphan receptor known as GCY-4, CKRL-3, or STRL-22 is a specific receptor for MIP-3α, and that its activation leads to pertussis toxin-sensitive and phospholipase C-dependent intracellular Ca2+ mobilization when it is expressed in HEK 293 cells.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 36 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:561593 HCAPLUS

DOCUMENT NUMBER: 127:233530

TITLE: Modulation of T-cell response to phospholipase A2 and phospholipase A2-derived peptides by conventional bee venom immunotherapy

AUTHOR(S): Kammerer, Regine; **Chvatchko, Yolande**; Kettner, Alexander; Dufour, Nathalie; Corradin, Giampietro; Spertini, Francois

CORPORATE SOURCE: Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, 1011, Switz.

SOURCE: Journal of Allergy and Clinical Immunology (1997), 100(1), 96-103
CODEN: JACIBY; ISSN: 0091-6749

PUBLISHER: Mosby-Year Book

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Immunol. mechanisms of desensitization are still incompletely understood. Safer methods of immunotherapy with reduced risks of anaphylaxis need to

be developed. To study the effects of conventional venom immunotherapy (VIT) on phospholipase A2(PLA2)-specific T cells and on T-cell reactivity to short and long synthetic peptides that map the PLA2 mol. Proliferation of a CD4+ cell-enriched peripheral blood mononuclear cell fraction and **cytokine** secretion by T cell lines from patients hypersensitive to bee venom and undergoing VIT in response to PLA2 and PLA2 synthetic peptides were measured. T-cell proliferation in response to three synthetic peptides, 40 to 60 amino acids long and mapping the entire PLA2 mol. with an overlap of 10 residues (1 to 59, 51 to 99, and 90 to 134) steadily increased during the first 14 wk of VIT corresponding to the treatment period with incremental doses of antigen. These results are in contrast to the low proliferation indexes obtained with short (15 amino acid-long) peptides, and the inability to characterize the immunodominant region of the mol. with short peptides. At the end of VIT (after 3 to 5 yr), there was correspondingly, a marked decrease in T cell responsiveness to PLA2 and to its long synthetic peptides. This response was paralleled by a shift in the pattern of **cytokine** secretion by T cell lines from a TH0-type to a TH1-type pattern. After a transient increase in T-cell proliferation, late VIT was characterized by T-cell hyporesponsiveness to allergen and by modulation of **cytokine** secretion from a TH0-type to a TH1-type pattern. Because of their capacity to recruit multiple T-cell epitopes, long peptides mapping the entire PLA2 mol. appear to be efficient T cell stimulators and may represent potential candidates for peptide immunotherapy.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 37 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:157019 HCAPLUS
DOCUMENT NUMBER: 126:237234
TITLE: Bacterial lipopolysaccharide rapidly inhibits expression of C-C chemokine receptors in human monocytes
AUTHOR(S): Sica, Antonio; Saccani, Alessandra; Borsatti, Alessandro; **Power, Christine A.**; Wells, Timothy N. C.; Luini, Walter; Polentarutti, Nadia; Sozzani, Silvano; Mantovani, Alberto
CORPORATE SOURCE: Istituto Ricerche Farmacologiche "Mario Negri", Milan, 20157, Italy
SOURCE: Journal of Experimental Medicine (1997), 185(5), 969-974
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study was designed to investigate the effect of bacterial lipopolysaccharide (LPS) on C-C chemokine receptors (CCR) expressed in human mononuclear phagocytes. LPS caused a rapid and drastic reduction of CCR2 mRNA levels, which binds MCP-1 and -3. CCR1 and CCR5 mRNAs were also reduced, though to a lesser extent, whereas CXCR2 was unaffected. The rate of nuclear transcription of CCR2 was not affected by LPS, whereas the mRNA half life was reduced from 1.5 h to 45 min. As expected, LPS-induced inhibition of CCR2 mRNA expression was associated with a reduction of both MCP-1 binding and chemotactic responsiveness. The capacity to inhibit CCR2 expression in monocytes was shared by other microbial agents and **cytokines** (inactivated Streptococci, Propionibacterium acnes, and to a lesser extent, IL-1 and TNF-α). In contrast, IL-2 augmented CCR2 expression and MCP-1 itself had no effect. Thus, regulation of

receptor expression in addition to agonist production is likely a crucial point in the regulation of the chemokine system.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 38 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:568203 HCAPLUS
DOCUMENT NUMBER: 125:218941
TITLE: Chemokine receptors - the new frontier for AIDS research
AUTHOR(S): Wells, Timothy N. C.; El Proudfoot, Amanda; **Power, Christine A.**; Marsh, Marsh
CORPORATE SOURCE: Geneva Biomedical Res. Inst., Glaxo Wellcome Res. and Development, Geneva, Switz.
SOURCE: Chemistry & Biology (1996), 3(8), 603-609
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Current Biology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 35 refs. CD4 is widely known as the HIV receptor, but is insufficient to allow viral infection. Recently, members of the family of chemokine receptors have been identified as the missing co-receptors, which act with CD4 to allow the virus to enter cells. These discoveries open up the possibilities of novel therapeutic strategies to combat HIV infection and AIDS.

L9 ANSWER 39 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:563504 HCAPLUS
DOCUMENT NUMBER: 125:212677
TITLE: Chemokine receptor cDNA sequence, binding by MCP-1, MIP-1α, and RANTES lymphokines, and treatment of allergy or atheroma
INVENTOR(S): Wells, Timothy Nigel Carl; **Power, Christine Anna**
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9623068	A1	19960801	WO 1996-GB143	19960124
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE				
AU 9644558	A1	19960814	AU 1996-44558	19960124
EP 805859	A1	19971112	EP 1996-900656	19960124
EP 805859	B1	20050420		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV				
JP 10513046	T2	19981215	JP 1996-522719	19960124
JP 2003038191	A2	20030212	JP 2002-141253	19960124
AT 293689	E	20050515	AT 1996-900656	19960124

US 6150132	A	20001121	US 1997-875573	19971031
US 2002187930	A1	20021212	US 2001-764413	20010119
US 6919432	B2	20050719		
US 2002160015	A1	20021031	US 2002-120394	20020412
US 2005014695	A1	20050120	US 2004-933356	20040903
PRIORITY APPLN. INFO.:			GB 1995-1683	A 19950127
			JP 1996-522719	A3 19960124
			WO 1996-GB143	W 19960124
			US 1997-875573	A1 19971031
			US 2000-614256	B1 20000712
			US 2001-764413	A1 20010119

AB A chemokine receptor binds to MCP-1, MIP-1 α and/or Rantes. It can be used in screening for agents which act as antagonists to MCP-1, MIP-1α and/or RANTES. Such agents may be useful in treating various disorders, including allergies, atheromas and diseases mediated by viruses. They may also be useful in preventing graft rejection and in protecting stem cells from potentially damaging effects of chemotherapy.

L9 ANSWER 40 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	1996:503485 HCAPLUS
DOCUMENT NUMBER:	125:165168
TITLE:	The molecular basis of the chemokine/chemokine receptor interaction-scope for design of chemokine antagonists
AUTHOR(S):	Wells, Timothy N. C.; Proudfoot, Amanda E. I.; **Power, Christine A.**; Lusti-Narasimhan, Manjula; Alouani, Sami; Hoogewerf, Arlene J.; Peitsch, Manuel C.
CORPORATE SOURCE:	Geneva Biomed. Res. Inst., GlaxoWellcome Res. Dev., Geneva, 1228, Switz.
SOURCE:	Methods (San Diego) (1996), 10(1), 126-134 CODEN: MTHDE9; ISSN: 1046-2023
PUBLISHER:	Academic
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	English

AB A review with 46 refs. Chemokines are a family of small proteins that are present in a variety of inflammatory conditions and have been shown to activate and recruit a wide variety of cell types. They bind to a family of seven transmembrane G-protein-coupled receptors. Models for the interaction of the chemokines with their receptors suggest a two-step mechanism. Initially, the main body of the chemokine interacts with the outside of the receptor (Site 1), and this interaction directs receptor selectivity. Subsequently, the flexible amino-terminus of the chemokine interacts with the receptor core (Site 2) to initiate the signaling response. Mutagenesis studies of IL-8, the archetypal CXC chemokine, show that altering the protein on the third β-sheet can change the receptor selectivity from that of a CXC chemokine and introduce CC chemokine activity-confirming the role of this region in Site 1. Mutagenesis studies of the amino-terminal region of IL-8 showed that a tripeptide, ELR, was essential for the interaction with Site 2. We have shown, using synthetic peptides and site-directed mutagenesis, that the amino-terminus of RANTES is important in the signaling response (Site 2). Mutations that alter only the interaction with Site 2 are capable of binding the receptor and not signaling and are therefore potential antagonists. Such antagonists have now been made by several groups, for a number of the chemokine receptors, and are active at nanomolar concns. These can now be used to test the hypothesis that antagonism of chemokine receptors will lead to a reduction in inflammation in vivo.

L9 ANSWER 41 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:433781 HCAPLUS
DOCUMENT NUMBER: 125:112106
TITLE: Cloning and characterization of human chemokine receptors
AUTHOR(S): **Power, Christine A.**; Wells, Timothy N. C.
CORPORATE SOURCE: Glaxo Inst. Mol. Biol., Geneva, Switz.
SOURCE: Trends in Pharmacological Sciences (1996), 17(6), 209-213
CODEN: TPHSDY; ISSN: 0165-6147
PUBLISHER: Elsevier Trends Journals
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 46 refs., including sections on CXC chemokine receptors, CC chemokine receptors, promiscuous receptors, virally encoded receptors, chemokine receptor-like orphan receptors, genomic localization, signaling pathways, and chemokine receptors in disease.

L9 ANSWER 42 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:367192 HCAPLUS
DOCUMENT NUMBER: 125:84186
TITLE: Cloning and characterization of a novel murine macrophage inflammatory protein-1α receptor
AUTHOR(S): Meyer, Alexndra; Coyle, Anthony J.; Proudfoot, Amanda E. I.; Wells, Timothy N. C.; **Power, Christine A.**
CORPORATE SOURCE: Glaxo Inst. Mol. Biol., Geneva, CH-1228, Switz.
SOURCE: Journal of Biological Chemistry (1996), 271(24), 14445-14451
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have cloned a novel CC chemokine receptor cDNA from mouse thymus. The deduced amino acid sequence shows 74% identity to the human monocyte chemotactic protein (MCP)-1 receptor (CC CKR-2b) and 54% to a recently cloned murine macrophage inflammatory protein (MIP)-1α receptor. Northern blot anal. of mouse tissues showed that the mRNA was also expressed in heart, spleen and liver, and to a lesser extent in lung and brain. The rank order of CC chemokine competition for 125I-labeled human RANTES (regulated on activation, normal T-cell expressed and secreted) binding to human embryonic kidney (HEK) 293 cells stably transfected with the receptor cDNA was murine MIP-1α » human MIP-1β > human RANTES > murine RANTES > murine MIP-1β > human MCP-2 > murine MCP-1 (JE) > human MIP-1α > human MCP-3 > human MCP-1. Of the chemokines tested, only murine MIP-1α, human and murine MIP-1β and RANTES, human MCP-2, and JE were able to induce mobilization of intracellular Ca2+ from fura-2-loaded HEK 293 cells expressing the receptor. These results suggest that this receptor functions as a high affinity murine MIP-1α receptor; however, it is likely to be an important target for the biol. activities of several CC chemokines in mouse.

L9 ANSWER 43 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:289034 HCAPLUS
DOCUMENT NUMBER: 125:83904
TITLE: A fluorescent interleukin-8 receptor probe produced by targetted labeling at the amino terminus. [Erratum to

document cited in CA122:184920]
AUTHOR(S): Alouani, Sami; Gaertner, Hubert F.; Mermod, Jean-Jacques; **Power, Christine A.**; Bacon, Keven B.; Wells, Timothy N. C.; Proudfoot, Amanda E. I.
CORPORATE SOURCE: Glaxo Inst. for Molecular Biology S. A., Geneva, CH-1228, Switz.
SOURCE: European Journal of Biochemistry (1996), 237(3), 882
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The errors were not reflected in the abstract or the index entries.

L9 ANSWER 44 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:102001 HCAPLUS
DOCUMENT NUMBER: 124:143290
TITLE: A molecular switch of chemokine receptor selectivity. Chemical modification of the interleukin-8 Leu25→Cys mutant
AUTHOR(S): Lusti-Narasimhan, Manjula; Chollet, Andre; **Power, Christine A.**; Allet, Bernard; Proudfoot, Amanda E.; Wells, Timothy N. C.
CORPORATE SOURCE: Glaxo Inst. Mol. Biol., Geneva, 1228, Switz.
SOURCE: Journal of Biological Chemistry (1996), 271(6), 3148-53
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Interleukin-8 (IL-8), a member of the CXC chemokine family, is a key activator of neutrophils. We have previously shown that two novel CC chemokine-like properties, namely monocyte chemoattraction and binding to CC CKR-1, are introduced into IL-8 by mutating Leu25 to the conserved tyrosine present in CC chemokines. To further investigate the role of this position in receptor selectivity, we have mutated Leu25 to cysteine. The protein folds correctly with two disulfide bonds and a free thiol group at Cys25. This mutant behaves overall like wild-type IL-8 receptor binding, and has no effect on CC CKR-1. These data are consistent with cysteine being approx. isosteric with the natural amino acid leucine. However, modification of the cysteine by addition of a fluorescent N-methyl-N-(2-N-Me, N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminoethyl)acetamido (NBD) group lowers potency in neutrophil chemotaxis and affinity in IL-8 receptor binding assays by 2 orders of magnitude. This Leu25 → Cys-NBD mutant introduces monocyte chemoattractant activity and the ability to displace 125I-labeled macrophage inflammatory protein-1α from the recombinant CC CKR-1 receptor. Addnl., we show a specific interaction between the fluorescent mutant and the N-terminal 34-amino acid peptide from CC CKR-1. This confirms the importance of this region in IL-8 in receptor binding and in conferring specificity between CXC and CC chemokines. CD spectra of the IL-8 mutants having CC chemokine-like activity show a consistent drop in α-helical content compared with the spectra for wild-type IL-8. This suggests that distortion of the C-terminal helix may play a role in chemokine receptor-ligand selectivity.

L9 ANSWER 45 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:90678 HCAPLUS

DOCUMENT NUMBER: 124:143254
TITLE: Extension of recombinant human RANTES by the retention of the initiating methionine produces a potent antagonist
AUTHOR(S): Proudfoot, Amanda E. I.; **Power, Christine A.** ; Hoogewerf, Arlene J.; Montjovent, Marc-Olivier; Borlat, Frederic; Offord, Robin E.; Wells, Timothy N. C.
CORPORATE SOURCE: Glaxo Inst. Molecular Biology, Geneva, Switz.
SOURCE: Journal of Biological Chemistry (1996), 271(5), 2599-603
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Extension of recombinant human RANTES by a single residue at the amino terminus is sufficient to produce a potent and selective antagonist. RANTES is a proinflammatory **cytokine** that promotes cell accumulation and activation in chronic inflammatory diseases. When mature RANTES was expressed heterologously in Escherichia coli, the amino-terminal initiating methionine was not removed by the endogenous amino peptidases. This methionylated protein was fully folded but completely inactive in RANTES bioassays of calcium mobilization and chemotaxis of the promonocytic cell line THP-1. However, when assayed as an antagonist of both RANTES and macrophage inflammatory polypeptide-1α (MIP-1α) in these assays, the methionylated RANTES (Met-RANTES) inhibited the actions of both chemokines. T cell chemotaxis was similarly inhibited. The antagonistic effect was selective since Met-RANTES had no effect on interleukin-8- or monocyte chemoattractant protein-1-induced responses in these cells. Met-RANTES can compete with both [125I]RANTES and [125I]MIP-1α binding to THP-1 cells or to stably transfected HEK cells recombinantly expressing their common receptor, CC-CKR-1. These data show that the integrity of the amino terminus of RANTES is crucial to receptor binding and cellular activation.

L9 ANSWER 46 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:77409 HCAPLUS
DOCUMENT NUMBER: 124:114734
TITLE: Selectivity and antagonism of chemokine receptors
AUTHOR(S): Wells, Timothy N. C.; **Power, Christine A.**; Lusti-Narasimhan, Manjula; Hoogewerf, Arlene J.; Cooke, Robert M.; Chung, Chun-wa; Peitsch, Manuel C.; Proudfoot, Amanda E. I.
CORPORATE SOURCE: Glaxo Institute Molecular Biology, Geneva, Switz.
SOURCE: Journal of Leukocyte Biology (1996), 59(1), 53-60
CODEN: JLBIE7; ISSN: 0741-5400
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 25 refs. The chemokine superfamily can be subdivided into two groups based on their amino terminal cysteine spacing. The CXC chemokines are primarily involved in neutrophil-mediated inflammation and, so far, two human receptors have been cloned. The CC chemokines tend to be involved in chronic inflammation, and recently the authors have cloned a fourth leukocyte receptor for this group of ligands. Understanding what makes one receptor bind its range of agonists is important if the authors

are to develop potent selective antagonists. The authors have started to investigate the mol. basis of this receptor selectivity by looking at why CC chemokines do not bind to the CXC receptors in several ways. First, the authors looked at the role of the three-dimensional structure of the ligand, and have solved the three-dimensional structure of RANTES using NMR spectroscopy. The structure is similar to that already determined for the CC chemokine macrophage inflammatory protein-1β, and it has a completely different dimer interface to that of the CXC chemokine interleukin-8 (IL-8). However, the monomer structures of all the chemokines are very similar, and at physiol. concns. the proteins are likely to be monomeric. Second, by examining all the known CC and CXC chemokines, the authors have found a region that differs between the two subfamilies. Mutations of one of the residues in this region, Leu-25 in IL-8, to tyrosine (which is conserved at this position in CC chemokines) enables the mutant IL-8 to bind CC-chemokine receptor-1 (CC-CKR-1) and introduces monocyte chemoattractant activity. Using other mutations in this region, the authors can show a direct interaction with the N-terminus of CC-CKR-1. Third, the authors have found that modification of the N-terminus of RANTES by addition of one amino acid makes it into an antagonist with nanomolar potency. Taken together, this data suggests a two-site model for receptor activation and for selectivity between CC and CXC chemokines, with an initial receptor contact provided by the main body of the chemokine, and activation provided by the amino terminal region.

L9 ANSWER 47 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:51863 HCAPLUS
DOCUMENT NUMBER: 124:115085
TITLE: Molecular cloning of murine CC CKR-4 and high affinity binding of chemokines to murine and human CC CKR-4
AUTHOR(S): Hoogewerf, A. J.; Black, D.; Proudfoot, A. E. I.; Wells, T. N. C.; **Power, C. A.**
CORPORATE SOURCE: Mol. Biol., Glaxo Inst., Geneva, Switz.
SOURCE: Biochemical and Biophysical Research Communications (1996), 218(1), 337-43
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have cloned the murine homolog of human CC Chemokine Receptor-4 (CC CKR-4). In equilibrium competition binding assays performed in undifferentiated HL-60 cells transfected with human and murine CC CKR-4 cDNA, the IC50 values for the binding of [125I]macrophage inflammatory protein-1α to human and murine CC CKR-4 were 14.5 nM and 10.1 nM, resp., and the IC50 values for the binding of [125I]RANTES to human and murine CC CKR-4 were 9.3 nM and 5.7 nM, resp. The cDNA clone for murine CC CKR-4 is 1531 bp, and the largest open reading frame encodes a protein of 360 amino acids that is 85% identical to human CC CKR-4. Murine CC CKR-4 was detected in the thymus and T-cell lines by Northern blot anal. This first report of direct binding of chemokines to CC CKR-4 demonstrates that the highly homologous human and murine receptors have similar binding characteristics and tissue distribution.

L9 ANSWER 48 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:976188 HCAPLUS
DOCUMENT NUMBER: 124:6830
TITLE: Characterization of the RANTES/MIP-1α receptor (CC CKR-1) stably transfected in HEK 293 cells and the recombinant ligands
AUTHOR(S): Proudfoot, Amanda E. I.; **Power, Christine A.**

; Hoogewerf, Arlene; Montjovent, Marc-Olivier; Borlat, Frederic; Wells, Timothy N. C.
CORPORATE SOURCE: Glaxo Institute for Molecular Biology, 14, Ch. des Aulx, 1228 Plan-les-Ouates, Geneva, Switz.
SOURCE: FEBS Letters (1995), 376(1,2), 19-23
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The CC chemokines RANTES and MIP-1α are known to activate certain leukocytes and leukocytic cell lines. We have produced and fully characterized the recombinant proteins expressed in E. coli. They induce chemotaxis of the pro-monocytic cell line, THP-1 and T cells. THP-1 cells express three of the known CC chemokine receptors. In order to study the activation of a single receptor, we have expressed the shared receptor (CC CKR-1) for RANTES and MIP-1α stably in the HEK 293 cell line. We have examined the effects of RANTES and MIP-1α on the CC CKR-1 transfectants by equilibrium binding studies and in a chemotaxis assay. RANTES competes for [125I]RANTES with an IC50 of 0.6 ± 0.23 nM, whereas MIP-1α competes for its radiolabeled counterpart with an IC50 of 10 ± 1.6 nM in the transfectants. These affinities are the same as those measured on the THP-1 cell line. The stably transfected HEK 293 cells respond to both these chemokines in the chemotaxis assay with the same EC50 values as those measured for THP-1 cells. This indicates that this cellular response can be mediated through the CC CKR-1 receptor.

L9 ANSWER 49 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:845225 HCAPLUS
DOCUMENT NUMBER: 123:254209
TITLE: Chemokine and chemokine receptor mRNA expression in human platelets
AUTHOR(S): **Power, Christine A.**; Clemetson, Jeanine M.; Clemetson, Kenneth J.; Wells, Timothy N. C.
CORPORATE SOURCE: Glaxo Institute for Molecular Biology, Geneva, 1228, Switz.
SOURCE: Cytokine (1995), 7(6), 479-82
CODEN: CYTIE9; ISSN: 1043-4666
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To study the role of platelets in inflammation the authors constructed a cDNA library from human platelet mRNA. By polymerase chain reaction (PCR) anal. of the library the authors have shown that platelets express mRNAs for the following chemokines: connective tissue activating peptide-III (CTAP-III), epithelial-derived neutrophil activating factor-78 (ENA-78), RANTES and monocyte chemotactic protein-3 (MCP-3). Platelets also express mRNAs for interleukin 8 receptor A (IL-8RA) and a novel chemokine receptor K5.5. These results suggest that chemokines may not only play an important role in platelet activation but can also influence the nature of the leukocyte infiltrate to sites of inflammation and infection, by the production of multiple chemokines with overlapping specificities.

L9 ANSWER 50 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:758326 HCAPLUS
DOCUMENT NUMBER: 123:307737
TITLE: Molecular cloning and functional expression of a novel CC chemokine receptor cDNA from a human basophilic cell line
AUTHOR(S): **Power, Christine A.**; Meyer, Alexandra;

Nemeth, Karin; Bacon, Kevin B.; Hoogewerf, Arlene J.; Proudfoot, Amanda E. I.; Wells, Timothy N. C.
CORPORATE SOURCE: Glaxo Inst. Mol. Biol., Geneva, CH-1228, Switz.
SOURCE: Journal of Biological Chemistry (1995), 270(33), 19495-500
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors report the cloning and characterization of a novel basophil CC chemokine receptor, K5-5, from the human immature basophilic cell line KU-812. The predicted protein sequence of K5-5 shows only 49% identity to the macrophage inflammatory protein-1α/RANTES receptor (CC CKR-1) and 47% identity to monocyte chemotactic protein-1 receptor (b form), suggesting that this cDNA encodes a novel member of the CC chemokine receptor family. Anal. of K5-5 mRNA expression indicates that it is restricted to leukocyte-rich tissues. In addition, the authors have shown significant levels of K5-5 mRNA in human basophils, which were up-regulated by treatment with interleukin-5. The CC chemokines, macrophage inflammatory protein-1α, RANTES, and monocyte chemotactic protein-1 were able to stimulate a Ca2+-activated chloride channel in Xenopus laevis oocytes injected with K5-5 cRNA, whereas no signal was detected in response to monocyte chemotactic protein-2, macrophage inflammatory protein-1β, or the CXC chemokine, interleukin-8. Taken together, these results indicate for the first time the presence of a CC chemokine receptor on basophils, which functions as a "shared" CC chemokine receptor and may therefore be implicated in the pathogenesis of basophil-mediated allergic diseases.

L9 ANSWER 51 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:497845 HCAPLUS
DOCUMENT NUMBER: 122:237508
TITLE: IL-8-induced signal transduction in T lymphocytes involves receptor-mediated activation of phospholipases C and D
AUTHOR(S): Bacon, Kevin B.; Flores-Romo, Leopoldo; Life, Paul F.; Taub, Dennis D.; Premack, Brett A.; Arkinstall, Stephen J.; Wells, Timothy N. C.; Schall, Thomas J.; **Power, Christine A.**
CORPORATE SOURCE: Glaxo Inst. Mol. Biol., Geneva, Switz.
SOURCE: Journal of Immunology (1995), 154(8), 3654-66
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have characterized the IL-8-induced signal transduction processes in T lymphocytes. A basal level of IL-8 receptor expression was shown on mixed PBL, as identified by using phycoerythrin (PE)-coupled IL-8, and this expression was increased following IL-2 stimulation. Scatchard anal. of T cells revealed competitive binding of IL-8 with a Kd of 0.55 nM, with approx. 1200 receptors per cell, on freshly isolated T cells. After 24 h in culture following purification, reverse transcriptase PCR (RT-PCR) analyses show the mRNA for only the type B IL-8R on these cultured T lymphocytes and the cell line MOLT-4. Stimulation of T lymphocytes or T cell clones with IL-8 led to generation of inositol trisphosphate and calcium flux. In addition, when T cells were prelabeled with [3H]oleic acid, IL-8 caused a long lasting, time- and dose-related increase in [3H]phosphatidylethanol (PtE), indicating activation of phospholipase D (PLD). By contrast, this

IL-8-dependent PLD activity was undetectable in IL-8-stimulated neutrophils. PLD activation appeared to be downstream of protein kinase C, because several inhibitors abrogated the increase in [3H]PtE, whereas guanosine-5'-O-(3-thiotriphosphate (GTP(γ)S)) and inositol trisphosphorothioate (IP3S3) both increased the generation of [3H]PtE. Together, these results demonstrate that the IL-8RB receptor is sufficient to mediate phospholipase C (PLC) and PLD activation in T lymphocytes, but not in neutrophils, and indicate an important difference in receptor usage and signal transduction pathways between IL-8-stimulated lymphocytes and neutrophils.

L9 ANSWER 52 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:400062 HCAPLUS
DOCUMENT NUMBER: 122:184920
TITLE: A fluorescent interleukin-8 receptor probe produced by targeted labeling at the amino terminus
AUTHOR(S): Alouani, Sami; Gaertner, Hubert F.; Mermod, Jean-Jacques; **Power, Christine A.**; Bacon, Keven B.; Wells, Timothy N. C.; Proudfoot, Amanda E. I.
CORPORATE SOURCE: Glaxo Inst. for Molecular Biology S. A., Geneva, CH-1228, Switz.
SOURCE: European Journal of Biochemistry (1995), 227(1/2), 328-34
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Interleukin-8 is the most extensively characterized member of the structurally related chemotactic and pro-inflammatory proteins collectively called chemokines. It binds to two closely related members of the seven transmembrane chemokine receptor family found on a variety of leukocyte cell types. To study the interaction of interleukin-8 with its receptors, and their distribution, the authors have produced a fluorescently labeled protein as an alternative to the radioactive 125I-interleukin-8 ligand. Interleukin-8 is naturally produced as two forms, a 72-residue polypeptide by monocytes and a 77-residue form produced by endothelial cells which has an extension of five amino acids at the amino terminal. Both forms are active at nanomolar concns., implying that chemical modification to the amino terminus of the 72-residue form will not destroy activity. The 72-residue interleukin-8 sequence starts with a serine residue, which can be oxidized under mild conditions to give a reactive glyoxylyl function which is then reacted with a nucleophilic fluorescein derivative The site-specifically labeled protein was easily isolated by reverse-phase HPLC. The dissociation constant of the fluorescently labeled interleukin-8 from its receptors on neutrophils was measured by displacement of 125I-interleukin-8 and was 10 nM compared to 1 nM for the unmodified protein. The modified protein is highly active in in vitro bioassays using human neutrophils, giving an EC50 of 7 nM in chemotaxis and an EC50 of 0.62 nM for shape change. The binding of the fluorescent protein to neutrophils can also be measured by fluorescent automatic cell sorter (FACS) anal., and can be competed by unlabeled interleukin-8. The amino-terminal modification of interleukin-8 has produced a reagent which is useful for the quantification of interleukin-8 receptor expression, and will also be useful in monitoring the fate of the ligand after receptor binding.

L9 ANSWER 53 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:366574 HCAPLUS

DOCUMENT NUMBER: 122:158298
TITLE: Mutation of Leu25 and Val27 introduces CC chemokine activity into interleukin-8
AUTHOR(S): Lusti-Narasimhan, Manjula; **Power, Christine A.** ; Allet, Bernard; Alouani, Sami; Bacon, Kevin B.; Mermod, Jean-Jacques; Proudfoot, Amanda E. I.; Wells, Timothy N. C.
CORPORATE SOURCE: Glaxo Inst. Molecular Biology, Plan-les-Ouates, 1228, Switz.
SOURCE: Journal of Biological Chemistry (1995), 270(6), 2716-21
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Interleukin-8 (IL-8) is a member of the CXC branch of the chemokine superfamily and activates neutrophils but not monocytes. The related CC chemokine branch, which includes monocyte chemoattractant protein-1 (MCP-1) and RANTES are potent chemoattractants for monocytes but not neutrophils. Examination of the sequences of the CXC chemokines reveals that the highly conserved leucine, corresponding to Leu25 in IL-8, is always replaced by tyrosine in CC chemokines. There is also a high degree of conservation among the CXC chemokines of the adjacent Val27 residue, which points out from the same side of the β-sheet as Leu25. In RANTES, Val27 is also replaced by a tyrosine. To investigate the role of these residues in controlling cell specificity, the authors have made the single mutants Leu25 → Tyr, Val27 → Tyr and the double mutant Leu25 → Tyr, Val27 → Tyr of IL-8. These proteins have been expressed in Escherichia coli and purified to homogeneity from inclusion body material. All three mutants have lower potency and efficacy in chemotaxis and calcium mobilization assays using neutrophils. The mutants also show lowered affinity to both IL-8 receptors A and B expressed recombinantly in HL-60 cells and to neutrophils in [125I]IL-8 competition assays. Addnl., the Leu25 → Tyr mutation introduces a novel monocyte chemoattractant activity into IL-8. The authors therefore studied the displacement of [125I]MIP-1α by IL-8 Leu25 → Tyr from the CC-CKR-1 receptor. The mutant displaces MIP-1α ligand with an affinity only 12-fold less than MIP-1α itself. This suggests that mutations in this region of IL-8 are involved in receptor binding and activation and in the control of specificity between CC and CXC chemokines.

L9 ANSWER 54 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:310313 HCAPLUS
DOCUMENT NUMBER: 122:237460
TITLE: Cloning of a full-length cDNA encoding the neutrophil-activating peptide ENA-78 from human platelets
AUTHOR(S): **Power, Christine A.**; Furness, Richard B.; Brawand, Carine; Wells, Timothy N. C.
CORPORATE SOURCE: Glaxo Institute for Molecular Biology, Plan-les-Ouates, Geneva, CH-1228, Switz.
SOURCE: Gene (1994), 151(1/2), 333-4
CODEN: GENED6; ISSN: 0378-1119
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A full-length cDNA encoding a neutrophil chemoattractant peptide, ENA-78,

was cloned from human platelets. The cDNA encodes a predicted sequence of 114 amino acids and contains the Cys motif C-X-C found in other members of the α-chemokine family which also includes interleukin 8 (IL-8). ENA-78 has a high degree of sequence identity with other platelet-derived chemokines which also share overlapping chemotactic activities such as GROα and the neutrophil-activating peptide 2 (NAP-2; derived by proteolytic cleavage of the connective-tissue-activating peptide III (CTAP-III)).

L9 ANSWER 55 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:262682 HCAPLUS
DOCUMENT NUMBER: 122:78801
TITLE: Eotaxin: cloning of an eosinophil chemoattractant **cytokine** and increased mRNA expression in allergen-challenged guinea pig lungs
AUTHOR(S): Jose, P. J.; Adcock, I. M.; Griffiths-Johnson, D. A.; Berkman, N.; Wells, T. N. C.; Williams, T. J.; **Power, C. A.**
CORPORATE SOURCE: Thoracic Med., Natl. Heart Lung Inst., London, SW3 6LY, UK
SOURCE: Biochemical and Biophysical Research Communications (1994), 205(1), 788-94
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Eotaxin was recently identified as the major eosinophil chemoattractant in bronchoalveolar lavage fluid obtained 3h after allergen challenge of sensitized guinea-pigs. The authors now report the cDNA cloning of this C-C chemokine. The 777 base-pair clone, pEo3122, consists of a 40 base 5' untranslated region, an open reading frame of 288 bases predicting a 73 amino acid mature protein plus a 23 amino acid signal peptide, and a 3' untranslated region of 449 bases containing a poly A tail. Northern blot anal. showed eotaxin mRNA in the lungs of naive and sensitized guinea-pigs, which was considerably increased after allergen challenge. Eotaxin may be an important mediator of eosinophil accumulation and activation in allergic reactions. As eotaxin stimulates human eosinophils, this chemokine and related mols. may be involved in human diseases such as asthma where eosinophil accumulation is a prominent feature.

L9 ANSWER 56 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:653453 HCAPLUS
DOCUMENT NUMBER: 121:253453
TITLE: Crystallization and preliminary x-ray diffraction studies of human RANTES
AUTHOR(S): Shaw, Jeffrey P.; Kryger, Gitay; Cleasby, Ann; Wonacott, Alan; **Power, Christine A.**; Proudfoot, Amanda E. I.; Wells, Timothy N. C.
CORPORATE SOURCE: Rosenstiel Basic Med. Sci. Res. Cent., Brandeis Univ., Waltham, MA, 02254, USA
SOURCE: Journal of Molecular Biology (1994), 242(4), 589-90
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The chemotactic **cytokine** RANTES is a potent chemoattractant and activator of a number of leukocytes, with a mol. mass of 8 kDa. Crystals of this protein have been grown from 100 mM sodium acetate buffer (pH 4.6)

containing 200 mM magnesium acetate, with 20% (w/v) PEG 4000 and 6% (volume/volume) glycerol. The crystals grow as thick rods, which diffract to at least 1.8 Å resolution on a rotating anode x-ray source. The crystals belong to space group P212121 with unit cell dimensions a = 95.14 Å, b = 57.58 Å, and c = 24.01 Å with α = β = γ = 90°. The asym. unit contains 2 mols. of the RANTES monomer, with a VM of 2.0 Å3/Da.

L9 ANSWER 57 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:555292 HCAPLUS
DOCUMENT NUMBER: 121:155292
TITLE: Interleukin-8 and RANTES induce the adhesion of the human basophilic cell line KU-812 to human endothelial cell monolayers
AUTHOR(S): Bacon, K. B.; Flores-Romo, L.; Aubry, J.-P.; Wells, T. N. C.; **Power, C. A.**
CORPORATE SOURCE: Glaxo Institute for Molecular Biology, Geneva, Switz.
SOURCE: Immunology (1994), 82(3), 473-81
CODEN: IMMUAM; ISSN: 0019-2805
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Basophils are implicated in the pathogenesis of the late-phase allergic reaction, but the mechanisms by which circulating basophils adhere to vascular endothelium and migrate to lesional sites remain unclear. In order to assess the biol. similarity of the basophilic cell line KU-812 to normal human basophils, the authors have compared the adhesion response of this cell line and normal basophils, following challenge with interleukin-8 (IL-8) and RANTES. The authors demonstrate here that IL-8 and RANTES are able to stimulate the adherence of the basophilic cell line, KU-812, to **cytokine**-activated human umbilical vein endothelium (HUVEC). The chemokine-induced increase in adhesion was dose-related and was maximal after prior priming with IL-5. The stimulation of adhesion was partially inhibited by co-incubation with anti-CD18 and anti-CD11c antibodies and antibodies to the β1-integrins. In comparison, the chemokine-induced adhesion of normal human basophils was only inhibited by the β2-integrins. These chemokines were also able to induce the migration of KU-812 in a dose-dependent manner, but only after prior treatment with phorbol myristate acetate (PMA) or IL-5. In all cases tested, IL-8 was more potent and efficacious than RANTES. The authors conclude from these studies that these members of the chemokine superfamily may play an important role in the recruitment of reactive leukocytes in allergic inflammation, by stimulating their adhesion and subsequent migration from the vasculature into the inflammatory sites. However, it is apparent that KU-812 is not an adequate substitute for normal human basophils in order to investigate chemokine biol.